deconditioning” in terms of cardiac responses to exercise in our patients, and phosphorus spectroscopy of muscle in the syndromes shown to consistent disturbance of muscle energy metabolism.1 The phenomenon may be of significance in the pathogenesis of “fatigue” in some patients, and it may be premature to conclude that neuromuscular function in all patients is normal, or that the “fatigue” is exclusively “central” in origin. Indeed, it may be pre- sumptuous to consider chronic fatigue syndrome as a unitary entity.

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PET assessment of brain metabolic recovery in aphasia

The paper by Cappa et al1 deals with the important issue of the mechanisms of recovery from aphasia. The authors longitudinally assessed two patients both neuropsychologically and by 18F-2-fluoro-2-deoxy-D-glucose ([18F-FDG]) PET measurements of the local cerebral metabolic rate of glucose (LCMRG1). Each patient was studied twice with a three month interval. The LCMRG1 values (19 brain regions on each side) were assessed for significant abnormali- ties at each study by comparison with values from a group of seven healthy sub- jects, while changes in LCMRG1 from first to second PET study were assessed in each patient individually by an analysis of variance with one between-factor (acute and chronic stage) and one within-factor (left and right hemisphere). The authors con- clude that (1) significant reductions in the LCMRG1 of many brain regions were present in both patients at initial evaluation, and in one patient at second evaluation only, and that (2) there was a significant increase in LCMRG1 from first to second evaluation in each of the two patients.

We wonder whether the statistical procedures used were appropriate. Firstly, regarding the comparison with the control group, Cappa et al used two standard devia- tions below control mean as the cut-off for p < 0.05; however, since the control group consisted of seven subjects, the two-tailed t value for six degrees of freedom, or 2.47, should have been used instead. As this value is substantially larger than 2.0, it is likely that several of the LCMRG1 values listed in tables 1 and 2 as statistically signifi- cantly reduced were, in fact, not.

In addition, the authors do not acknowledge the fact that there is a multiple testing problem as they are simultaneously assessing the type 1 error of all regions. Secondly, the analysis of variance proce- dure used to assess changes in LCMRG1 from one study to the next in each subject is of serious concern. Apparently, it was run on the 19 regional values for each side of the brain, two determinations, and yielded inordinately low probability levels (down to < 0.0001) for single subject stud- ies. Their way of using the analysis of vari- ance in this and another study1 would appear inadequate and possibly misleading.

The authors do not point out the fact that region must also be a within-subject factor. In the case of measurements of LCMRG1, there exists a global scaling factor (the mean brain CMRG1), itself influenced by both physiological and methodological factors, that affects all regional values of a given subject. Thus, in the comparison of the two sets of LCMRG1 data obtained in a single subject at two sequential studies, any change in this global factor will be repeated over all brain regions. While the regions analysed, the larger the degrees of freedom and, in turn, the more statistically significant the findings. One way of turning around this problem would have been to normalize for this global factor by, for example, an analysis of covariance.

When studying the changes in brain metabolism in a longitudinal fashion, more appropriate ways of testing whether a sig- nificant change in LCMRG1 has occurred from one investigation to the next would be to assess each brain area either across a suffi- ciently large group of patients or, in single subjects, by taking the numerical changes observed against confidence limits estab- lished for the same region in a set of control subjects studied twice at similar time inter- vals (that is, confidence limits for reproduc- ibility). The results presented by Cappa et al regarding recovery of LCMRG1 must therefore be taken as descriptive only, pend- ing confirmation from a better designed investigation.

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Cappa et al reply:

Drs Baron and Ford express their concern about the appropriateness of the statistical methods used to support the major findings of our paper, namely that (1) a sig- nificant reduction in cerebral metabolic rate for glucose was present in several regions, not only of the right, but also of the left hemisphere in two patients with crossed aphasia in the acute stage; and (2) a significa- nt increase of metabolism occurred between the first and the second examina- tion, three months after onset, in the same two patients.

Baron and Ford consider a cut off value equal to the mean minus two standard devi- ations of LCMRG1 of normal controls as inadequate, and suggest the use of the two- tailed t value for six degrees of freedom (2.47 SD). We think that the choice of a two-tailed value is questionable, as patho- logical values can a priori be expected to lie at the lower tail of the distribution (in the latter case, the cut off can be calculated as 1.645 SD—that is, approximately a one-tailed value used in our paper). Nevertheless, we have re-analysed our data using this ultra- conservative approach. Even adopting this criterion, the main finding of bihemispheric metabolic reduction and limits ourselves to the regional results were only marginally different (case 1—examination I: no change, examination II: right 04 and 05 and left T3, T8, and T9 above the cut off; case 2—examination I: right and left T3, T4, T8, and T9 above the cut off). On the other hand, it is noteworthy that the latter values also fall below the fifth centile of the distribution of normal values from a larger set of normal controls, which has been collected in our laboratory after the comple- tion of this study.

We have proposed that region should have been included as a within-sub- ject factor in the analysis of variance. This design would, of course, be the most infor- mative in the study of the regional corre- lation of function. However, the characteristics of our sample, however, (two cases, with a very low probability to increase sample size within a reasonable time span), we had to forsake the important issue of regional effects and limit ourselves to the assessment of changes in hemispheric metabolism between the baseline evaluation and the follow up study in a 2 × 2 factorial design. We thus think it advisable to remove “global” effects on the hemispheric values in this context would be questionable, given that the mean global cerebral metabolic rate is necessarily affected by intrahemispheric and transhemispheric diaschisis, namely, by the phenomenon under scrutiny.

Having said that, we appreciate that the description of two single cases is, by definition, “descriptive”. Given the limited cur- rent understanding of crossed aphasia and the absence of other instances of atypical cerebral dominance, to ascribe further explanatory power to our observations was far fetched.

The methodological suggestions by Baron and Ford, however, are rather impractical. To collect a “sufficiently large number of patients”, given the incidence of crossed aphasia, would require a dedicated multi- centre study. For radioprotection reasons, in some countries it would be difficult to perform two repeated studies with [18F-FDG] in normal subjects within three months.

We have proposed that patients with crossed aphasia may be particularly liable to distant effects, due to their bilateral lan- guage representation. Larger studies of the clinical correlations of distant effects and of their relationships with lesion characteris- tics, as well as with patient related variables (such as age, gender, handedness) are war- ranted to prove or disprove this specific hypothesis.

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